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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/731,467	12/07/2000	Charles Jack Fisher	X-12448A	6830

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/27/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/731,467	FISHER ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-20 are still at issue and are present for examination.

Applicants' amendments and arguments filed on 10-9-01, paper No.3, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glas-Greenwalt et al. (J. Lab Clin. Med., 1986, Vol. 108:415-422) Gruber et al. (Circulation, 1990, Vol. 82:578-585), Foster et al. (US 5,516,650, 5-14-1996). Claims 1-5 in this instant application are drawn to a method of treating a patient suffering from thrombotic thrombocytopenic purpura (TTP) comprising the administration of a pharmaceutically effective amount of protein C (PC) wherein the PC is human zymogen, human activated PC and wherein the amount of activated PC is about 1-96 microgram/kg/hr and wherein the activated PC is administered by continuous infusion for about 1 to 240 hours. Please see previous Office action for the rejection.

In response to the previous Office action, applicants have traversed the above rejection arguing that Examiner has failed to set forth a *prima facie* case of obviousness as the combination of references cited by the Examiner is due to impermissible hindsight reasoning and not by a suggestion or motivation to modify or combine these references. Examiner respectfully disagrees and submits that Examiner has indeed shown that the above references render the

claims *prima facie* obvious to one of ordinary skill in the art and that Examiner has not resorted to any hindsight reasoning as alleged by the applicants.

Applicants argue that they discovered an important and previously unknown method for treating TTP and HUS using protein C, human protein zymogen or human activated protein C. Examiner has shown through these references that the use of protein C for above disorders was quite well known in the art. Applicants argue that Glas-Greenwalt teaches the technique of plasma exchange (PE) and that while protein C is present in plasma, the technique of PE is not used for supplementing protein C. Applicants also argue that PE did not affect protein C levels alone and that it affected other plasma factors and that the reference does not lead the reader to believe that protein C alone affects TTP. Applicants also argue that plasma also contains components beyond just protein C. While Examiner agrees with the applicants that the protein C alone in the exchanged plasma may not contribute to the positive effects of PE, Examiner disagrees with the applicants that the reference does not lead the reader to believe that protein C levels has any effects at all. This is because the skilled artisan would clearly be aware that PE using plasma from a normal donor would supplement or elevate levels of protein C in such patients as the protein C levels in the donor plasma would be at normal levels. Furthermore, the reference also clearly describes the role of protein C and that its deficiency is associated with thromboembolic diseases (page 420 column 2) thus motivating one skilled in the art to elevate levels of protein C at least as one of the method of treatment for thromboembolic diseases.

The reference of Gruber et al. lends more support for the obviousness rejection than Gras-Greenwalt et al. Applicants argue that Gruber et al. involves the use of recombinant activated protein C (rAPC) to inhibit thrombus formation in baboons and not human patients and therefore not obvious to extend the use of rAPC to humans. Examiner respectfully disagrees with such an argument. It is well known in the area of medical research, that results from animal model experiments form the foundation for human trials or treatments. Applicants

arguments that the results obtained from an animal model experiments does not render the human trials as obvious is misplaced. Also, applicants argument that the dosages taught by Gruber do not extend to human treatment and that the high dosages that provide promising results in baboons are highly likely to result in serious adverse events in humans is also highly misplaced and simply does not over come the obvious ness rejection. This is because applicants are arguing as if each reference used in an obviousness rejection must teach each and every limitation of the instant claims. Applicants are reminded that for a prima facie obviousness it is only the combination of references which must teach or suggest the limitation of the claims. Examiner has clearly explained in his rejection, that using the results from the baboon experiments, it would have been obvious to those skilled in the art to come up with appropriate dosages for humans such that it would not be lethal. Applicants also argue about etiology for TTP as due to severe infection. It is not clear to the Examiner as to how that argument would help in overcoming the above rejection. Severe infection is not a limitation in the instant claims and is also not the part of the reference. Applicants also argue that the baboon model does not teach about reversal of organ dysfunction or reduced mortality for humans. Here again as these are not claim limitations, it is not clear to Examiner as how such an argument would help in overcoming the above rejection. Therefore contrary to applicants argument, the above reference motivates one of ordinary skill in the art to use protein C to treat TTP related disorders.

Applicants have taken the Foster et al. reference out of context. Examiner used the above reference to show the availability of recombinant Protein C and the motivation to use a recombinant product. Applicants have argued that the reference methods are directed to modified human protein C and that there is no suggestion or motivation to modify this reference to treat TTP and that Foster's teachings are in no way linked to applicants' invention involving a method of treating a patient using protein C. Examiner respectfully disagrees with the applicants. As stated earlier, Examiner has used this reference to show the availability of

recombinant protein C in the art. Foster et al. while not explicit, does teach that "in view of the clinical applicability of human protein C and human activated protein C in the treatment of thrombotic disorders (it would be clear to one of ordinary skill in the art that "thrombotic disorders" encompasses TTP and HUS) the production of human protein C and human activated protein C by recombinant techniques is clearly invaluable". Furthermore the argument by the applicants regarding modified human protein C taught by Foster et al. is again highly misplaced. This is because applicants claims are not specifically drawn to unmodified protein C or a specific protein C with a specific sequence identification. As such the instant claims encompasses all types of protein C including those modified, unmodified, natural or recombinants. Therefore contrary to applicants argument the above reference in combination with that of Gruber et al. does motivate one of ordinary skill in the art to use recombinant protein C for treatment of thrombotic disorders.

In response to rejection of claims 6-20 as obvious over Glas-Greenwalt et al. (J. Lab Clin. Med., 1986, Vol. 108:415-422) Gruber et al. (Circulation, 1990, Vol. 82:578-585), Foster et al. (US 5,516,650, 5-14-1996) as applied to claims 1-5 above, and further in view of Hollenbeck et al. (Nephrol. Dial. Transplant., 1998, Vol. 13:76-81), applicants have traversed the rejection. Applicants while agreeing that Hollenbeck et al. teach that TTP and HUS are considered as one entity because of similarities in clinical and morphological findings, traverse the rejection arguing that the above references in combination does not render the invention obvious. Applicants again reiterate their arguments regarding plasma exchange. Applicants argue that PE is not a means for protein C supplementation. Here again, applicants appear to be arguing out of context. Examiner has used the reference of Hollenbeck to show that relation between TTP and HUS and that they are one and the same occurring in different individuals. Even though applicants down play the reference of Hollenbeck and the role of plasma exchange as a technique to restore protein C levels, it would have been obvious to one of ordinary skill in

the art to extend the results obtained from the experiments of Gruber et al. for use in treatment of HUS as Hollenbeck teach that HUS and TTP are identical disorders.

Applicants vehemently argue that cited references do not disclose nor even suggest using protein C for treatment of TTP and HUS in humans and that the references are directed to four separate concepts none of which add up to the instant invention even if a suggestion to modify or combine had been asserted. Examiner respectfully disagrees with such a conclusion of the applicants. For the sake of argument, if Glas-Greenwalt reference was not considered, the above invention would have been obvious to one of ordinary skill in the art just by combination of the teachings of Gruber et al. and Foster et al. The Gruber et al. teaching regarding the use of protein C in baboons and the provision of recombinant protein C by Foster et al. would have also motivated one of ordinary skill in the art to extend the results to humans as therapy. With the positive outcome in baboons, one of the closest genetic relative of humans, one of ordinary skill in the art would have a reasonable expectation of success for extending the use of protein C in humans, rendering the above invention *prima facie* obvious. Applicants argument that Foster et al. teach a modified protein C adds no weight to the argument because instant claims are not limited to non-modified protein C. Applicants argument that the invention claims a particularized dose and plasma level as well as means of administration *via* continuous infusion and /or bolus injection and that the references do not teach the same is totally misplaced. This is because the establishment of a dosage regimen and the methods of administration are all well within the skill of those practicing the art and does not in any way render the claims non-obvious. As all the references teach either fully or in part the beneficial effects of protein C, applicants allegation that Examiner has resorted to hindsight reconstruction of the invention is baseless. Therefore for all the above reasons the above rejection is maintained.

Conclusion

Conclusion

None of the claims are allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.

Manjunath N. Rao
December 18, 2002

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600